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10/577,124	05/01/2007	Gary Robinson	05794.00003	1425

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EXAMINER	
PORTNER, VIRGINIA ALLEN	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
07/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/577,124	ROBINSON ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 8-41* is/are pending in the application.

4a) Of the above claim(s) *9-29 and 31-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 8, 30,41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 3-5, 8-41 are pending. Claims 1, 3-5, 8, 30, 41 are under consideration; all other claims stand withdrawn from consideration as being drawn to a non-elected invention.

Objections/Rejections Withdrawn

2. ***Claim Objections*** The objection to claim 38 for depending from both claims 12 and 37 simultaneously and is a "Use" claim which is a non-statutory category of invention is herein withdrawn, in light of Applicant withdrawing the claim from consideration and is no longer will be considered for examination.

3. ***Drawings*** The objection to the drawings for failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description, specifically SEQ ID NOs in the Brief Description of the Drawing for the sequences shown in Figure 1, has been obviated by amending the instant Specification Brief Description of the Drawing to recite the needed SEQ ID NOs.

4. Claim Rejections - 35 USC § 101 The rejection of Claim 30 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966), is herein withdrawn in light of the amendment of claim 30 to depend from claim 1 or claim 3.

5. The rejection of claim 1, 3-5, 8, 30, 37 under 35 U.S.C. 102(b) as being anticipated by Kende et al US PG-Pub 2003/0095985 is herein withdrawn in light of the amendment of the independent claim to an anti-LuxR antibody which is not taught or suggested in Kende et al.

6. Claim 11 is no longer objected to for not complying with the requirements of 37 CFR 1.821 because Applicant has amended the amino acid sequence to recite a SEQ ID NO.

Information Disclosure Statement

7. The information disclosure statement filed April 28, 2010 has been considered.

Objections/Rejections Maintained

8. Applicant's arguments filed April 28, 2010 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. The rejection of claims 1,3,5 8, 30, 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Ulrich et al (US PG Pub 2004/0171020, filing date July 15, 2002) in light of extrinsic evidence provided by Kolibachuk et al (1993) is traversed by asserting that:

a. "The disclosures of Ulrich et al. are based on and entirely consistent with the erroneous belief held in the art at the filing date of the present invention that LuxR and its homologues were intracellular proteins.

b. Ulrich et al. suggests preparation of antibodies to AHS transcriptional regulator (i.e., LuxR). However, the suggestion to provide such antibodies is in the context of detection of AHS transcriptional regulators (LuxR) and not in the context of regulation of quorum sensing.

3. It is the position of the Office that Kolibachuk et al in 1993, about 9 years before the filing date of Ulrich et al, taught LuxR and LuxR homologs to be membrane associated proteins for binding to autoinducer prior to intracellular synthase activation. LuxR clearly functions both at the membrane level to bind to autoinducer, as well as functions intra-cellularly to regulate transcription.

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The *Vibrio fischeri* Luminescence Gene Activator LuxR Is a Membrane-Associated Protein

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4. While it is true that Ulrich et al teach methods of detecting a LuxR homolog containing bacterial cell in a sample with an antibody,

Ulrich et al *goes beyond* teaching just assay methods of detection to methods of modulating or inhibiting LuxR activity with an antibody, the antibody being "provided as an isolated and substantially purified protein[0093}" for the purpose of reducing or inhibiting the activity of the synthase transcriptional regulator protein.

The polyclonal or monoclonal antibodies are formulated and administered by standard routes [0093, 0094]. The full size polyclonal and monoclonal antibodies of Ulrich would not cross the bacterial cell membrane.

Ulrich et al teach an embodiment that administers antibodies to a subject and the antibodies would bind to the LuxR homolog associated with the cell membrane of the gram negative bacteria, in light of evidence provided by Kolibachuk et al who teach that LuxR and other LuxR homologs have joined the "growing list of membrane associated transcription factors in prokaryotes".

> Finally, this report, indicating that LuxR is associated with membranes of *V. fischeri*, adds another transcriptional activator to a growing list of membrane-associated transcription factors in prokaryotes (6, 7, 22, 32, 35, 47, 51, 52). These membrane-associated transcription factors do not form a group based on amino acid sequence alignments. However, it should be pointed out that many of these transcription factors respond to environmental signals related to an association with an animal or plant host. For example, LuxR is responsive to cell density as mediated by autoinducer, and this allows expression of luminescence in a specific light organ symbiosis; NodD in *R. leguminosarum* activates genes involved in root nodule formation in response to its interaction with flavonoid compounds produced by the plant host (for a recent review see reference 46); and ToxR in *Vibrio cholerae* is a transmembrane protein that activates the gene encoding cholera toxin in response to an environmental signal (10, 34).

page 7311, column 2, p. 2

While Ulrich et al does not recite the term "biofilm inhibition", the reference carries out the claimed method steps with antibodies specific for a LuxR homolog for the purpose of modulating gram negative bacterial growth, or inhibition of bacterial growth. The inhibition of bacterial growth is the same or equivalent process as inhibiting biofilm formation as bacterial growth is the source of biofilm formation and the antibodies of Ulrich et al serve to inhibit bacterial growth.

Ulrich et al still inherently anticipates the instantly claimed invention as now claimed in light of evidence provided by Kolibachuk et al who teach LuxR homologs are membrane associated, and the anti-LuxR antibodies (antibodies directed to synthase transcriptional regulator, LuxR homolog) are disclosed for administration to a subject in vitro (cells), ex vivo or in vivo [0105] for modulation (reducing or inhibiting) synthase transcriptional regulator activity.

5. The rejection is maintained for reasons of record and responses set forth herein.

New Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1,3-4, 8, 30, , 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Taga et al (US PG-Pub 2003/0165932, publication date Sept. 4, 2003, reference cited in US PTO 892 dated December 30, 2009) in light of evidence provided by Kolibachuk et al (1993).

Taga et al disclose the instantly claimed method, the method comprising the steps of:

Claims1. An extracellular method of regulating quorum sensing in bacteria expressing LuxR or a homologue thereof (LsrR "[0325] Identification of LsrR: a protein responsible for mediating AI-2 regulation of transcription of the lsr operon."), said method comprising modulating [0244 "inhibit the activation of bacterial pathways associated with virulence"], the activation by a signaling molecule of LuxR or a homologue thereof by

Administering [0185-187, 0244-0245, 0249, 0298] to said bacteria an antibody([0018, 0146, 0132])

"[0018] With respect to **antibodies** of the invention, the term "immunologically specific" refers to **antibodies** that bind to one or more epitopes of a protein of interest, but that do not substantially recognize and bind other compounds in a sample containing a mixed population of antigenic biological constituents. "

"[0146]**LsrR** protein has SEQ ID NO: 36)."

"[0132] 73. An **antibody** that binds to a polypeptide selected from the group consisting of SEQ ID NOs.: 36"

[0249] Thus, the invention includes various pharmaceutical compositions useful for ameliorating symptoms attributable to a bacterial infection …. pharmaceutical composition according to the invention can be prepared to include an **antibody** against…..**LsrR**, ….., a peptide or peptide derivative of ……, **LsrR**, …. mimetic, ...".

which specifically binds LuxR or the homologue thereof [0244], wherein the binding of an antibody to a homologue of LuxR (see claim 73; [0291]) prevents said homologue of LuxR from being activated by its signaling molecule ([0243 "inhibits the activity of AI-2, the transport of AI-2 into the cell,"]), and "can inhibit the activation of bacterial pathways associated with virulence. [0244]")

"[0244] ….. **Antibodies** raised to LsrA, LsrB, LsrC, LsrD, LsrE, LsrF, LsrG, **LsrR**, LuxP or LuxQ or homologues thereof, can inhibit the activation of bacterial pathways associated with virulence. Thus, LsrA, LsrB, LsrC, LsrD, LsrE, LsrF, LsrG, **LsrR**, LuxP or LuxQ provide common antigenic determinants that can be used to immunize a subject against multiple

pathogen-associated disease states. For example, the autoinducer Signaling System type-2 is believed to exist in a broad range of bacterial species including bacterial pathogens. As discussed above, the autoinducer-2 signaling factor is believed to be involved in interspecies as well as intraspecies communication. In order for the quorum sensing Signaling System type-2 to be effective for interspecies communication, it is likely to be highly conserved among various bacterial species. Thus, challenging a subject with the LsrA, LsrB, LsrC, LsrD, LsrE, LsrF, LsrG, **LsrR,** LuxP or LuxQ polypeptide, or an antigenic fragment thereof, isolated from a particular organism may confer protective immunity to other disease states associated with a different organism. …". [0249]

Claim 3. The method according to claim 1 wherein said bacteria are Gram negative [0005-0006].

Claim 4. The method according to claim 1 or claim 3 wherein said homologue of LuxR is LasR

[0291], or LuxS.

Claim 8. The method according to claim 1 wherein said antibody is a monoclonal antibody

"[0291] LsrA, LsrB, LsrC, LsrD, LsrE, LsrF, LsrG, or **LsrR** proteins, proteins homologous thereto or **antibodies** that recognize the foregoing proteins may also be prepared as described above. " [0290] The present invention also provides **antibodies** capable of immunospecifically binding to the **LuxS**-encoded protein of the invention. **Polyclonal antibodies** may be prepared according to standard methods. In a preferred embodiment, **monoclonal antibodies** are prepared, which react immunospecifically with various epitopes of the protein. **Monoclonal antibodies** may be prepared according to general methods of Kohler and Milstein, following standard protocols. **Polyclonal or monoclonal antibodies** that immunospecifically interact with the **LuxS**-encoded proteins can be utilized for identifying and purifying such proteins. For example, **antibodies** may be utilized for affinity separation of proteins with which they immunospecifically interact. **Antibodies** may also be used to immunoprecipitate proteins from a sample containing a mixture of proteins and other biological molecules."

Claim 30.The method according to claim 1, wherein the binding of an antibody inhibits biofilms

[0258] It is known that quorum sensing blockers can reduce protease production by 50% in some strains of bacteria but the discovery that certain compounds can substantially eliminate protease production imparts clear clinical advantages. Furthermore, the unexpected finding that biofilm formation can be inhibited or prevented by quorum sensing blockers leads to the reasonable conclusion that other quorum sensing

blockers that are known to exhibit quorum sensing blocking in other systems, such as protease production, will also be effective against biofilm formation. "

Claim 41. The method of claim 1, wherein said antibody is unable to cross the bacterial cell membrane.

[0049 "External AI-2 signals to the LsrR protein"] "[0140] The mechanism of AI-2 signaling to **LsrR** to derepress transcription of the lsr operon can be from the inside or **the outside of the cell**."

Toga et al anticipate the instantly claimed invention as now claimed in light of extrinsic evidence provided by Kolibachuk et al who teach LuxR and LuxR homologs are known to be membrane associated and proteins for binding to autoinducer prior to intracellular synthase activation. (see Kolibachuk et al , 1993)

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert B Mondesi/
Supervisory Patent Examiner,
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July 7, 2010